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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,547	10/17/2001	Jim Wells	SUNESIS.002DV1	8070

20995 7590 05/25/2005

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 05/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,547	WELLS ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 Feburary 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,59,61-66 and 81-96* is/are pending in the application.

4a) Of the above claim(s) *62-64,66,90-92 and 94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58,59,61,65,81-89,93,95 and 96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/28/05 has been entered. Claims 58, 59, 61-66, 81-96 were pending. No claims were added, deleted and/or amended. Therefore, claims 58, 59, 61-66 and 81-96 are currently pending. Claims 62-64, 66, 90-92 and 94 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Consequently, claims 58, 59, 61, 65, 81-89, 93, 95 and 96 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

3. Claims 58, 59, 61, 65, 81-89, 93, 95 and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (WO 98/11436) (Date of Patent is **March, 1998**)

(see IDS, entry No. 9) and Siuzdak (Siuzdak, G. Mass Spectrometry for Biotechnology. New York: Academic Press. **1996**, pages 119-126) and Jindal et al. (WO/9701755) (Filing Date is June 26, **1995**).

For ***claims 58, 86-87***, Kim et al. (see entire document) disclose a method for identifying a ligand that binds to a target protein with the greatest affinity by employing a combinatorial library of non-oligomeric organic compounds using "tethering" techniques (see Kim et al., page 1, paragraph 1; see also page 2, paragraphs 1-2). For example, Kim et al. disclose **[a]** combining said target protein with a library containing at least two non-oligomeric ligand candidates wherein said ligand candidates each comprise a disulfide bond under disulfide exchange conditions, in the presence of a reducing agent (e.g., see Kim et al., see also page 11, paragraph 2, "As obtained, a target molecule might also include a binding partner (such as a sulfur moiety within a cysteine residue) which is available or can be made available (e.g., as a free sulfhydryl group or sulfur that is available for disulfide bond formation through exchange) for binding with a reactive moiety. If such a target molecule is used, potential ligands [i.e., at least 2] can be modified to include a free sulfhydryl group or a sulfur that is available for disulfide bond formation through exchange ... Here, non-specific binding of target molecule and potential ligands occurs through formation of a disulfide bond"; see also page 17, paragraph 1 disclosing the use of reducing agents, "non-specific interaction (here, disulfide bond formation) can be varied by adjusting the concentration of external ... reducing agents ... for example ... glutathione").

Furthermore, Kim et al. disclose the formation of a target protein-ligand conjugates (e.g., see Kim et al., claims 1-2; see also page 3, paragraphs 2-3; see also page 9, line 14; see also page 14, paragraph 1; see also page 28, paragraph 1, "This experiment illustrates under conditions wherein a specific interaction between a target molecule and ligand can take place, preferential formation of disulfide-mediated ligand-target heterodimers [i.e., a target protein-ligand conjugate] can be observed"). Furthermore, Kim et al. disclose that the target-ligand conjugate can be separated from the mixture (e.g., see Kim et al., page 3, lines 24-26, "Optionally, the complex of the ligand specifically bound to the target molecule can be separated or removed from the library or collection").

In addition, Kim et al. disclose **[c-d]** the detection of the "most abundant" target protein-compound conjugates and the identification of the non-oligomeric organic compounds present in said conjugates having the "greatest relative affinity" (e.g., see Kim et al., page 17, lines 16-25, "The direct thermodynamic relationship also provides an alternative strategy for identifying ligands from a combinatorial library; molecules that bind with ***higher affinity*** will necessarily increase the effective concentration of the other members of the binding pair to a greater extent. Thus, in this embodiment, tethered ligands that bind with higher affinity will have disulfide bonds that are ***more resistant to reduction*** by external reducing agents, such as reduced glutathione"; see also Example 1, especially page 26, last paragraph wherein Glutathione is used in different "ratios" to determine the ligand with the highest affinity, "The biotinylated SH3 domain derivatives and the corresponding synthetic linkers (SH3 : linker; 1:10) are

incubated with the library of compounds, in Tris buffer (10 mM, pH 7.5), in the presence of a redox system (e.g., reduced glutathione (GSH) and oxidized glutathione (GSSG) ***at various ratios***"). In other words, only the non-oligomeric organic ligands with the "highest affinity" will remain resistant to the highest "ratios" of reduced/oxidized glutathione. Consequently, the method would also identify the most abundant target protein-compound conjugate because, at least for the highest ratios of reduced/oxidized glutathione, the conjugate formed using the "non-oligomeric organic compound having the greatest relative affinity" would be the only one that exists at the higher rations or reduced/oxidized glutathione. Finally, Kim et al. disclose "determining the identity" of the non-oligomeric ligand present in said target protein-ligand conjugate (e.g., see Kim et al., abstract, "Non-specific affinity enhancement as a method of identifying and detecting members, such as ligands ... in a collection or library of potential ligands"; see also Summary of the Invention; see also page 8, lines 18-20).

For ***claims 59, 61, 88 and 89***, Kim et al. does not explicitly state that the ligands are "less than about 2000 daltons in size" or "less than 1500 daltons " or "less than 750 daltons" (see claims 58, 59 and 61), but Kim et al. does disclose ligands selected from the group consisting of "small organic molecules, pharmaceuticals, toxins" (see Kim et al., page 21, lines 15-20; see also claim 3 further disclosing "steroids, hormones, caffeine, ATP, cyclosporin, cyclophilin"), which would encompass molecules that are less than 750 daltons in size. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are

not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 65 and 93***, Kim et al. does not explicitly state that the target protein is a "TNF receptor" (e.g., see claim 65), but Kim et al. does disclose ligands that are "membrane proteins", which would encompass proteins like TNF receptors because TNF receptors are "membrane proteins" (e.g., see claims 12, 43). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 81, 82***, Kim et al. teach obtaining a target protein comprising a –SH group, masked –SH group, or activated –SH group (e.g., see Kim et al., claims 1-2, "target molecule, as obtained or as modified, contains one member of a binding pair ... wherein the binding partner and the reactive moiety are each a free sulfhydryl group [i.e., an –SH group] or a sulfur moiety which is available for disulfide bond formation through exchange"; see also page 3, paragraphs 2-3; see also page 11, line 11 wherein a "cysteine" residue is disclosed).

For ***claims 83-85, 95 and 96***, Kim et al. do not explicitly state that the library must comprise "at least 25 members" or "at least 100 members" (see claims 84-85), but Kim et al. do state that libraries are produced using the split and pool synthesis techniques taught by Lam (e.g., see Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J., "A new type of synthetic peptide library for identifying ligand-binding activity" Nature **1991**, 354, 6348, 82-4), which teaches the formation of libraries with greater than 100 members. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The prior art teachings of Kim et al. differ from the claimed invention as follows:

For ***claim 58 and 86***, Kim et al. is deficient in that it does not specifically teach the use of mass spectrometry.

However, the combined references of Siuzdak and Jindal et al. teache the following limitations that are deficient in Kim et al.:

For ***claims 58 and 86***, the combined references of Siuzdak (see entire document) and Kim et al. (see entire document) teach the use of electrospray mass spectrometry to study both "non-covalent" and "covalent" antibody-antigen

interactions including fragmentation techniques like MS^2 and MS^3 (see pages 119-126, especially figures 6.3-6.6 and Table 6.1). In addition, the combined references of Siuzdak and Kim et al. teach that mass spectroscopy may be applied to "combinatorial libraries" of targets and/or ligands for screening purposes (e.g., see Jindal et al., Field of Invention, "This invention relates to ... rapid analysis of solutions of a large number of mixed molecular species, commonly called "libraries" ... to select ligands having a desired affinity for a target molecule of interest"; see also page 13, lines 2-7; see also figures 1-2, element 44; figures 3-4, element 136; figure 7A-D).

It would have been obvious to one skilled in the art at the time the invention was made to "identify" target/ligand interactions using the "affinity enhancing" techniques as taught by Kim et al. with mass spectroscopy as taught by the combined references of Siuzdak and Jindal et al. because Jindal et al., for example, explicitly state that mass spectrometry can be applied to the study of target/ligand interactions including the use of combinatorial libraries (e.g., see Jindal et al., Field of Invention), which would encompass the libraries disclosed by Kim et al. (i.e., the references represent analogous art). In addition, a person of skill in the art would have been motivated to use mass spectroscopy as disclosed by the combined references of Siuzdak and Jindal et al. because Jindal et al., for example, state that their technique improves upon the prior art by increasing the speed by which the target/ligand interactions can be screened, facilitating the use of automation, increasing the sensitivity of the method, and provides enough information about the ligand to facilitate its molecular

"identification" thus preventing the need for further characterization by some other analytical technique (e.g., see Jindal et al., page 5, paragraphs 1-2, "Accordingly, the present invention is directed to rapid, efficient and automated ... methods ... for screening libraries to select ... a candidate ligand ... for a preselected target molecule" Additionally, the present invention ... overcomes the disadvantages of the methods known in the art"; see also page 3, lines11-24, "Screening methods known in the art thus are not entirely satisfactory ... existing systems are unable selectively to screen a library while simultaneously determining the affinity of selected ligands for the target ... [another] major hurdle [that has been overcome by the present invention] ... is effective chemical characterization of ligands identified in these processes ... A major focus ... is to enable the collection of enough of or enough information about a ligand of interest so as to permit determination of its structure [i.e., using mass spectroscopy]"). Furthermore, Jindal et al. explicitly state that mass spectroscopy is the method of choice for studying libraries (e.g., Jindal et al., page 26, lines 12-15, "The integrated coupling of various dimensions such as ... electrospray ionization mass spectrometry in an automated multi-dimensional system should permit a highly sensitive and highly selective approach to decoding complex mixtures [i.e., mass spectroscopy is the method of choice for libraries]"). Finally, a person of skill in the art would reasonably have been expected to be successful because both Jindal et al. and Kim et al. state that their screening methods are widely applicable to a wide range of target/ligand interactions (e.g., both

references disclose the use of small molecule pharmaceuticals, phage libraries, peptide, proteins, antibody/antigen, etc.).

In addition, Siuzdak explicitly shows that the technique can be applied to both "covalent" and "non-covalent" including antibody-antigen interactions (e.g., see Siuzdak, figures 6.3, 6.5; see especially paragraph bridging pages 125-126, "Electrospray mass spectrometry has also demonstrated its potential in the analysis of non-covalent interactions between an antibody and a hapten, and for observing covalent protein-bound intermediates in an antibody-catalyzed reaction"), which would encompass the "antibody-antigen" complexes disclosed by Kim et al. (e.g., see Kim et al., page 4, lines 7-8 disclosing antibody-antigen reactions; see also lines 18-19 disclosing both "covalent" and "non-covalent" interactions). Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Siuzdak with the antibody-antigen conjugates as taught by Kim et al. (or any other target-ligand interaction) because Siuzdak explicitly states that electrospray has "demonstrated its potential" for these systems (see Siuzdak, page 126, paragraph 1).

In addition, one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Siuzdak et al. with the "antibody-antigen" complexes as described by Kim et al. because Siuzdak et al. discloses that BOTH "covalent" and "non-covalent" interactions can be measured (and distinguished) using a mass spectrometer (see Siuzdak et al., page 123, paragraph 3, "Declusterin potentials on the order of 70 V or greater usually promote the dissociation of noncovalent complexes as well as covalent fragmentation, while lower potentials

(<70 V) are conducive to the observation of noncovalent complexes (protein complexes have been analyzed at declustering potentials of 40 V). In order for the method of Kim et al. to work the modified antibodies must bind "covalently" to their respective antigens (see Kim et al., figure 1 disclosing the covalent attachment of an antigen to a sulfhydryl group on the modified antibody). Therefore, any analytical technique that can confirm the "covalent" attachment of the antigen to the modified antibody is particularly useful. Consequently, a person of skill in the art would be motivated to "identify" even a "known" ligand using a mass spectrometer to determine the type of interaction (i.e., covalent v. non-covalent) to ascertain whether the modified ligand is truly able to bind to its respective target via a "covalent" bond as required by the method. Consequently, a person of skill in the art would be motivated to search for the "modified" ligands and/or targets as disclosed by Kim et al. with electrospray mass spectroscopy as disclosed by Siuzdak et al. to find modified ligands that can "covalently" bind to the targets as opposed to any unwanted "non-covalent" interactions that might occur.

Finally, one of ordinary skill in the art would have reasonably expected to be successful because Siuzdak (just like Jindal et al. and possibly hundreds to thousand of other references that are too numerous to list in this rejection) shows many examples of target-ligand interactions that have successfully been analyzed on a mass spectrometer including antibody-antigen (e.g., see figures 6.3 and 6.5).

Response

4. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "According to paragraphs 3 and 5, Dr. Siuzdak disagrees with the Examiner's conclusion that his statement that '[e]lectrospray ionization mass spectrometry has also demonstrated its potential ... for observing covalent protein-bound intermediates in an antibody-catalyzed reaction' would have motivated one skilled in the art to identify a novel ligand by the mass spectrometry detection of a covalently bound protein-ligand conjugate in a mixture ... In paragraph 6, Dr. Siuzdak goes on explaining that '[w]hile electrospray ionization mass spectrometry is well suited to study enzymatic mechanisms where all of the participants are known, its use to analyze mixtures of unknown components is limited.' One reason for this is that 'heterogeneous compounds can produce complicated spectra that can be difficult or impossible to interpret.' Another obstacle is that 'heterogeneous mixtures tend to reduce the sensitivity of electrospray ionization mass spectrometry'" (e.g., see 2/28/05 Response, pages 1-3; see also Declaration by Dr. Gary Siuzdak).

This is not found persuasive for the following reasons:

The Examiner respectfully disagrees. Although Dr. Gary Siuzdak is unquestionably an expert in the field of mass spectrometry, his position in this particular case does not seem to be supported by the art. Dr. Siuzdak distinguishes the use of mass

spectroscopy as it is applied to "known" targets and/or ligands (like in his book) from those that are "unknown" and/or otherwise found in "complicated" mixtures such as combinatorial libraries (as in the present application). To refute this assertion, the Examiner sets forth in the newly amended rejection the Jindal et al. reference (as previously cited in the advisory action), which clearly shows that mass spectroscopy was "routinely" applied to "unknown" targets and/or ligands including "complicated" mixtures like combinatorial libraries (e.g., see newly amended rejection above and quotations cited therein). Furthermore, the Examiner reiterates that the Siuzdak reference is only one of potentially hundreds if not thousands of references that support this position (e.g., see 12/20/04 advisory action, which is incorporated in its entirety herein by reference).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 17, 2005